PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 17026 KB	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/HU2004/000037	International filing date *(day/month/year)* 14.04.2004	Priority date *(day/month/year)* 15.04.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/4355, A61K31/155, A61K31/427, A61K31/64, A61P3/00, A61P3/10

Applicant
SYNOSENS KUTATO ES FEJLESZTO KFT. et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.11.2004	18.04.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/HU2004/000037

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-21	as originally filed
1a	filed with telefax on 14.02.2005

Claims, Numbers

1-10	filed with telefax on 14.02.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Re Item V

A combination of cicletanine and an anti-diabetic or anti-hyperlipidemic agent selected from the group listed in claim 1 b) for treating type 2 diabetes mellitus, insulin resistance, dislipidemia and polycystic ovary syndrome is neither disclosed nor suggested in the cited prior art (Art. (Art. 33 (1),(2),(3) PCT).

Re Item VI

The applicant's attention is drawn to the following **when entering the European regional phase**.

In newly filed claim 7 the applicant has introduced a disclaimer: "with the proviso that said states related to (...) are other than diabetic nephropathy".

However, a disclaimer may be only allowable in order to:

- restore novelty by delimiting a claim against an **accidental anticipation** (an anticipation is accidental if it is so unrelated to and remote from the claimed invention that the person skilled in the art would never have taken it into consideration when making the invention)

- disclaim subject-matter which is excluded from patentability for non-technical reasons.

A disclaimer which is or becomes relevant for the assessment of **inventive step** or sufficiency of disclosure adds subject-matter.
(see decisions G1/03 and G2/03)

In this case D1, which was published in August 1999 and which **cannot be considered an accidental disclosure**, discloses the use of cicletanine for treating diabetic nephropathy (i.e. a state related to hyperglycemia and/or insuline resistance).
The same applies to documents D2-D3.

Thus the introduction of the disclaimer in claim 7 is not admissible (Art. 19 (2) PCT).

The applicant should limit the claim to the specific diabetic complications listed on page 20, lines 14-18 of the description as filed.

Claims:

1. A synergistic pharmaceutical combination suitable for the prevention or treatment of a prediabetic state, metabolic X-syndrome or type 2 diabetes mellitus as well as disorders which are associated with the states listed above, namely insulin resistance, dislipidemia and/or polycystic ovary syndrome comprising

(a) a first pharmaceutical composition containing cicletanine or a pharmaceutically suitable acid addition salt thereof and one or more conventional carrier(s), and

(b) a second pharmaceutical composition containing an antidiabetic or anti-hyperlipidemic active agent selected from the group consisting of metformin, troglitazone, glyburide or a pharmaceutically suitable acid addition salt thereof and lovastatin, and one or more conventional carrier(s).

2. A pharmaceutical combination of Claim 1 in which a single pharmaceutical composition comprises both the cicletanine or a pharmaceutically suitable acid addition salt thereof and the antidiabetic or anti-hyperlipidemic active agent or a pharmaceutically suitable acid addition salt thereof.

3. A pharmaceutical combination of Claim 1 or 2 comprising cicletanine or the hydrochloride thereof and metformin or a pharmaceutically suitable acid addition salt thereof.

4. A pharmaceutical combination of Claim 1 or 2 comprising cicletanine or the hydrochloride thereof and troglitazone.

5. A pharmaceutical combitanion of Claim 1 or 2 comprising cicletanine or the hydrochloride thereof and glyburide.

6. A pharmaceutical combitanion of Claim 1 or 2 comprising cicletanine or the hydrochloride thereof and lovastatin.

7. Use of cicletanine or a pharmaceutically suitable acid addition salt thereof for the preparation of a pharmaceutical composition to treat states related to hyperglycemia and/or insulin resistance, with the proviso that said states are other than diabetic nephropathy.

8. The use of Claim 7 in which the state is metabolic X-syndrome.

9. The use of Claim 6 in which the state is type 2 diabetes mellitus.

10. The use of Claim 6 in which the state is a prediabetic state.

Duran et al. disclosed that cicletanine had a nephro-protective effect on the progression of renal disease in a hypertensive and diabetic rat model. Another result of the research was that treatment with cicletanine did not affect significantly hyperglycemia in animals [Duran, M.J. et al., European Heart Journal, 20, 422 (1999)].

Kohzuki et al. examined the renal and cardiac benefits of cicletanine and stated that the drug had a renal-protective effect. However, treatment with cicletanine did not improve diabetes in diabetic rats and did not affect urinary and blood glucose concentrations at the dose employed [Kohzuki, M. et al., Am. J. of Hypertension, 13, 298-306 (2000)].

Bringer et al. evaluated antihypertensive drugs to be administered to diabetic patients and stated that cicletanine used as monotherapy in moderated hypertension had the advantage not to interfere with the glycemic or lipid equilibrium [Bringer, J. et al., Revue Francaise d'Endocrinologie Clinique – Nutrition et Metabolisme 1992 France, 33, 337-345 (1992)].

Bayés et al. investigated the possible interaction between cicletanine and the hypoglycemic drug tolbutamide, however, no clinically relevant interaction was found [Bayés, M.C. et al., Eur. J. Clin. Pharm., 50, 381-384 (1996)].

Thus, it could be concluded that cicletanine did not have any influence on glycemia.